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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/151,409	09/10/1998	JAMES B. DALE	481112.410	7693

500 7590 07/26/2002

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	32

DATE MAILED: 07/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/151,409	Dale
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

The MAILING DATE of this communication appears on the cover sheet with the correspondence address

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 1, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44, and 54-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44, and 54-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO AFTER-FINAL AMENDMENT

Applicant's After-Final Amendment

1) Acknowledgment is made of Applicant's supplemental after-final amendment filed 07/01/02 (paper no. 31) in response to the final Office Action mailed 03/26/02 (paper no. 27), which amendment has been entered. With this, Applicant has amended the specification.

Status of Claims

2) Claims 12, 15-17, 19, 21, 23, 27, 36-38, 40, 42, 44, 54 and 56 have been amended via the amendment filed 07/01/02.

Claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-58 are pending and are under examination.

Withdrawal of Finality

3) The finality of the Office Action mailed 03/26/02 (paper no. 27) is hereby withdrawn, partly in view of the newly discovered reference(s) to Hruby *et al.* Rejection(s) based on the newly cited reference(s) follow.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

6) The objection to the drawings made in paragraph 1 of the Office Action mailed 05/26/99 (paper no. 11) is maintained for reasons set forth therein. Applicant is asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit

number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible.

Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Objection(s) Withdrawn

7) The objection to the specification made in paragraph 6 of the Office Action mailed 03/26/02 (paper no. 27) is withdrawn in light of Applicant's amendment to the specification.

Rejection(s) Withdrawn

8) The rejection of claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 49-58 made in paragraph 15 of the Office Action mailed 03/26/02 (paper no. 27) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

9) The rejection of claims 12 and 27 made in paragraph 16(a) of the Office Action mailed 03/26/02 (paper no. 27) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

10) The rejection of claims 15-17, 19, 21, 23, 30-32, 34, 36-38, 40, 42, 44 and 49-58, made in paragraph 15 of the Office Action mailed 03/26/02 (paper no. 27) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph

11) Claims 12, 15, 17, 19, 21, 23, 27, 30-32, 34, 36, 38, 40, 42, 44, 54, 55, 57 and 58 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a recombinant fusion polypeptide comprising at least two immunogenic polypeptides obtained from Group A streptococcal M protein that are capable of eliciting an immune response against Group A Streptococci, does not reasonably provide enablement for a recombinant fusion polypeptide comprising any two 10 amino acid-long polypeptides other than the one obtained from Group A streptococcal M protein, as claimed in a broad sense.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;

  The relative skill of those in the art;

  The predictability or unpredictability of the art; and

  The breadth of the claims.

In the instant case, the specification teaches a recombinant fusion polypeptide obtained from Group A streptococcal M protein of the recited serotypes of Group A streptococci, wherein at least two decamer polypeptide of the M protein and a carboxy terminal reiteration of the same from the amino terminal of the immunogenic portion elicits an immune response against Group A streptococci. Outside this scope, however, a recombinant fusion polypeptide comprising a multivalent immunogenic portion comprising at least 10 amino acid-long Group A streptococcal non-M protein polypeptide that is capable of eliciting an immune response against Group A streptococci and a carboxy terminal reiteration of the at least 10 amino acid-long non-M protein (Group A streptococcal) polypeptide that protects the immunogenicity of the immunogenic portion is not enabled. No non-Group A streptococcal M protein carboxy terminal polypeptide that protects the immunogenicity of the immunogenic portion wherein the carboxy terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino terminal of the immunogenic portion is disclosed. Group A streptococci produce several different polypeptides other than the M protein. Whether or not these non-M protein polypeptides of Group A streptococci can be reproducibly produced recombinantly as a fusion polypeptide is not known. Whether or not any two 10 amino acid-containing fragments of any non-M protein of Group A streptococci serotype 1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18,1 9, 22, 24, 28, 30, 48, 49, 52 or 56 when expressed along with a carboxy terminal reiterated polypeptide would retain the capacity to elicit an immune response against Group A streptococci is neither disclosed nor predictable. Therefore, due to the lack of adequate disclosure and/or specific guidance, the lack of predictability, the lack of working examples enabling the full scope of the claims, the breadth of the claims and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to practice the full scope of the invention as claimed. Instant claims are viewed as not meeting the scope of enablement provisions of the 35 U.S.C § 112, first paragraph.

To obviate the rejection, it is suggested that Applicant limit the scope of 'immunogenic polypeptides' in claims 12 and 27 to --immunogenic polypeptides obtained from Group A streptococcal M protein--.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) Claims 16, 37, 56 and 57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claims 16, 37 and 56 are vague and indefinite in the recitation "M protein" without reciting its source. It is unclear whether this protein is the M protein of Flavi virus, Sendai virus, Group A streptococci or any other microorganism. To obviate the rejection, it is suggested that Applicant replace the recitation "M protein" with --Group A strteptococcal M protein--.

(b) Claim 57, which depends from claim 56, is also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 103

13) Claims 12, 15, 27 and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hruby *et al.* (*PNAS* 88: 3190-3194, 1991) in view of Marston *et al.* (In: *Methods in Enzymology, Guide to Protein Purification*. (Ed) MP Deutscher. vol. 182, section 20, pages 264-276, 1991).

Hruby *et al.* teach a recombinant CRR protein comprising the C-repeat region (CRR) from the carboxyl half of a *Streptococcus pyogenes* M protein containing from 1 to >20 tandem copies of the CRR region. The protein is detergent soluble (see abstract; and Figure 4). The recombinant protein obtained from VV:CRR3X contains multiple copies of the CRR of the M6 molecule responsible for cross-protection against streptococcal pharyngeal colonization (see page 3191, left column, lines 1-3; and right column). The protein derived from a recombinant construct contains at least two copies of 104 amino residue-long (i.e., at least 10 amino acid-long) M protein CRR segments in the 5' to 3' direction. See Figure 1. The number of CRR in the recombinant product, n, equals 1-20. Thus, as is evident from Figure 1A and 1B, Hruby's recombinant protein expressed by the VV:CRR3X construct contains a carboxy terminal CRR segment (i.e., polypeptide) that is a reiteration of a copy of the CRR segment from the amino terminal portion of the recombinant product.

Hruby *et al.* differ from the instant invention in not teaching the expression of multivalent CRR of the *Streptococcus pyogenes* M protein as a fusion polypeptide.

However, the expression of a polypeptide as a fusion polypeptide is well known and routinely practiced in the art of immunology/microbiology. For instance, Marston *et al.* teach the construction of polypeptides by gene fusion for the purpose of facilitating efficient purification (see page 275 and 176).

It would have *prima facie* been obvious to one skilled in the art at the time the invention was made to express Hruby's recombinant multivalent CRR protein as a fusion polypeptide using art known techniques to produce the instant invention with a reasonable expectation of success. Given the routine teaching Marston that expression of a polypeptide in the form of a fusion polypeptide facilitates purification, a skilled artisan would have been motivated to produce the instant invention for the expected benefit of facilitating the efficient purification of Hruby's polypeptide.

Claims 12, 15, 27 and 36 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

14) The prior art made of record and not currently relied upon in any rejection is considered pertinent to Applicants' disclosure:

- Dale (US 6,419,932) discloses recombinant hybrid (i.e., fusion) streptococcal M protein antigens, and vaccines comprising the same that elicits immunity against Group A streptococci. The carrier elicits antibodies (therefore immunogenic) and has or is a C-repeat portion of a streptococcal M protein, such as, M5 protein (see abstract and claims). One or more C-repeats of the M protein can be used as the carboxy terminal portion in the construct (see column 8, fifth full paragraph). The DNA molecules encoding the hybrid constructs code for amino or carboxy terminal fragments of the M protein that contain epitopes which elicit opsonic or protective antibodies against types 1, 3, 5, 6, 14, 18, 19, 24, 27 or 29 M proteins (see column 6, lines 41-45). Dale's ('932) invention includes hybrid constructs containing repeating amino-terminal or carboxy-terminal M protein fragments produced using PCR (see column 10, lines 1-3). The invention provides an antigen comprised of a carrier, which constitutes the carboxy-terminal portion of a serotype of M protein fused directly to an amino acid fragment of M protein, wherein the carrier and fragment may be of the same or different serotype (see column 3, lines 47-51). The vaccine is present in acceptable diluents or adjuvants readily known to one of

skill in the art, such as, Freund's adjuvant (see column 11, second full paragraph; and column 14, lines 14 and 15). The antibodies elicited by the vaccine are opsonic to the targeting serotype, but not cross-reactive with mammalian heart tissue antigens (see column 5, fourth full paragraph). That Dale's ('932) repeating carboxy-terminal carrier M protein fragments represent the instantly claimed immunogenic portion comprising at least two immunogenic polypeptides wherein the carboxy terminal polypeptide serves as a reiteration of at least one immunogenic polypeptide from the amino terminal of the immunogenic portion is inherent from the disclosure of Dale ('932).

- Vashishtha *et al.* (*J. Immunol.* 150: 4693-4701, May 1993) teach that the C-repeats located within the C-terminal half contain epitopes **conserved** among over 30 different M serotypes (see page 4693, right column). Vashishtha *et al.* teach that the widely shared epitopes located in the C-repeat region of the molecule induce protection (see page 4694).

Remarks

15) Claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-58 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER